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EXAMINER	
FEISEE, L	
ART UNIT	**PAPER NUMBER**
1806	13

18M2/0526

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DATE MAILED: 05/26/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 2/7/94 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. 2 pages
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-14, 17-18 are pending in the application.
   Of the above, claims 17-18 are withdrawn from consideration.
2. ☒ Claims 15, 16 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-14 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Newly submitted claims 17 and 18 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: These claims are drawn to method of treating diabetes by using adhesion molecules and fibronectin which is classified in class 514 subclass 12+. The claims which were elected for production were methods of treating diabetes by administering antibodies which are classified in class 424 subclass 85.8. Additionally, the methods currently presented and the methods originally elected differ in their reagents and method parameters.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 17 and 18 are withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

Cancellation of claims 15 and 16 is acknowledged and all rejections pertaining to these claims are rendered moot.

The rejection of claims 1-14 under 35 USC 112 second paragraph is withdrawn.

Claims 1-14 remain rejected under 35 USC 112 first paragraph for reasons previously set forth in paper # 7.

With respect to the language "prior", it is maintained that the broad range of this term lacks enablement in the specification. Applicant asserts that this language can be defined as when the serum glucose level is less than 250 mg/dl. This in itself is broad since less than 250 mg/dl reads on 0 mg/dl or 249 mg/dl. The specification has only shown a protective effect of a single antibody R1-2 on adoptive transfer of diabetes wherein NOD mice were treated with the antibody periodically for 30 post transfer. Applicant has not established a correlation of this information to humans. Additionally, applicant has not provided information as to whether the treatment would be effective if the serum glucose levels are at, for example, 249 mg/dl, which is a level prior to the presentation of overt diabetes. The claims as drafted read on embodiments which have not been supported in the specification.

Further, the duration of treatment is only represented by a single antibody and is therefore not commensurate in scope with the broadly claimed invention. The information based on a single antibody is not predictive of the use of any or all anti-VLA4 antibodies for human therapy. (see paper #7 pages 5-7).

Applicant further asserts that NOD mice are accepted models for human type I diabetes. This is not found to be persuasive because the use of an animal model to study the pathogenesis of a disease, as is the case of the NOD mouse with respect to

diabetes, is quite different from the use of an animal model to predict the efficacy of drugs in humans. As previously stated applicant has not established that NOD mice are predictive of the utility of anti-VLA4 antibodies as human therapeutic agents.

With respect to the lack of enablement of antibody fragments of antibodies for treating diabetes, the previous action stated reasons why not all fragments of antibodies would be useful in therapy. For example, although, the specification discusses Fab, Fab' $F(ab)_2$ and FV fragments, the claims are drawn to any or all fragments of antibodies beyond those disclosed. The binding affinity of antibody fragments may be different than whole antibodies, or the removal of the effector portion of the antibody may result reduced or the lack of effectiveness of antibodies. Since the mechanism of function of these particular antibodies is not elaborated, it is not clear what effect the use of the various fragments would have on the efficacy of the antibody. Additionally, fragments of antibodies include non-binding fragments that may have no effect on the activity of the antibody in treating diabetes. Applicant has not established that the exemplified antibody is enabled in the specification much less the fragments which comprise it.

The rejection of claims 1-14 under 35 USC 101 is maintained for reasons of record (paper #7, pages 5-7).

Applicant relies on the examples in the specification to

show utility in humans. As mentioned above, applicant has not established a link between NOD mice and human with respect to the therapy of diabetes. Neither the declaration Dr. Burkely nor the Yang et al. reference add new information with respect to the predictiveness of therapeutic agents in NOD mice, rather they simply reassert that this model is accepted as model for diabetes. The declaration and the reference present additional evidence which would be convincing if the animal model were predictive of the efficacy of therapeutic agents in humans. This has not been established other than through assertion. Applicant is again reminded that the use of an animal model for the study of pathogenesis, ie. the progression and commencement of a disease is not equal to the use of an animal model to predictability evaluate therapeutic agents.

With respect to Waldmann and Harris, it should be noted that these references were cited to show the general state of the art pertaining to antibody therapeutics. There is no question that there are a few isolated successes concerning the use of antibodies in in vivo therapy, however, these are the exceptions and not the rules. Applicant attempts to rebut the two references as not showing the general state of the art by presenting four articles. The first article, which shows the effective use of OKT3 is an exception which shows therapeutic efficacy using anti-CD3 antibodies. The second article of Knox

et. al. basically shows that a single anti-CD4 antibody was shown to have promise for clinical use. In fact, the authors themselves state that "chimeric anti-CD4 may [emphasis added] prove to be of use for the treatment of CD4 positive lymphoid malignancies." (page 29, first column, last paragraph). This reference does not show statistically significant data for evaluating therapeutic efficacy.

The third reference, Kirkham et. al., states that variable response is noted in using chimeric CD7 mAbs to treat rheumatoid arthritis and that chimeric anti-CD7 "functions' in vivo, but makes no statement that this mAb is useful for the therapy of rheumatoid arthritis.

The final article, Moreland et. al., also do not proclaim that cM-T412 is a useful antibody for therapy of refractory arthritis, rather they cautiously state that this antibody may be effective therapy for RA pending further experiments (see page 316, last paragraph columns 1 and 2). None of these antibodies establish that antibody-based reagents are predicted to work in humans, rather, they support the examiners assertion that antibodies must be evaluated on a case by case basis. There is no doubt that potential for antibody-based therapeutic agents exists, but for now , the art suggests that the success of a single or even a few antibodies for therapy of a single disease is not predictive of all antibodies.

With respect to Harris, it should be noted that not only does Harris discount the use of rodent antibodies in vivo, but he also states that chimeric antibodies have also proven to be disappointing as they elicit unwanted anti-variable region responses. In conclusion, although isolated success exists with antibodies in human therapy, they are too few and too far in between to lead on of ordinary skill in the art to immediately believe the utility of an antibody without convincing evidence.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lila Feisee whose telephone number is (703) 308-2731.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Feisee/em
May 04, 1994
May 26, 1994

DAVID L LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180

5/26/94